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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/244,195	02/04/1999	GEORGE BARRIE KITTO	D6073	3475

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BENJAMIN A. ADLER
8011 CANDLE LANE
HOUSTON, TX 77071

EXAMINER
PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/03/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/244,195	KITTO, G. B., AND M. S. BURNET	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

Detailed Office Action

37 C.F.R. § 1.114

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

2. Acknowledgement is hereby made of receipt and entry of the submission filed 11 March, 2003. No amendments to the claims accompanied the response. Claims 1-2 and 5-11 are pending in the instant application.

35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by

the same person or subject to an obligation of assignment to the same person.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

5. Claims 1, 2, and 5-11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). As previously set forth, Brey *et al.* (1992) describe the preparation of S. *typhimurium* expression systems (including those derived from strain SL3261) that are useful for the expression of heterologous (e.g., malaria) antigens. A detailed description of suitable expression vectors can be found in Table 1 and column 20. This publications also discloses that said expression systems are particularly useful because the vectors of interest retain their enteroinvasive properties but are markedly reduced in terms of virulence. This properties make these vectors particularly useful for generating both humoral and cell-mediated immune responses against the antigen of interest (see col. 7, first paragraph). Various vaccine formulations can be prepared and routes of administration utilized (i.e., oral, intradermal, intramuscular, intraperitoneal, intranasal, etc.) (see col. 21, section 5.6). A particularly attractive feature of this vector

system is the ability of S. *typhimurium* to invade the gut epithelial tissue thereby leading to strong mucosal and helper immune responses (see cols. 23 and 24, section 5.6.2). Other advantages of this vector system include the lack of a necessary purification step for the immunogen of interest and the ability of this system to be inexpensively produced and conveniently administered. The probability of adverse reactions in both animals and humans is also low. This teaching does not disclose the utilization of an Lpp-OmpA-Tat fusion protein.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene.

Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. For instance, see columns 3-7 of the Haseltine publication wherein the gene, expression vectors, and cell lines producing said protein are described. The Kang publication describes the preparation of HIV-1 Tat-expressing recombinant baculoviruses (see col 8, first

paragraph). Finally, Rodman describes the preparation of recombinant Tat and its utilization in ELISA assays (see col. 15). Thus, these teachings all illustrate that HIV-1 Tat was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Response to Arguments

6. Applicants traverse and submit that the combination of references do not render the claimed invention obvious and that there was no reasonable expectation of success. Applicants' argue that Haseltine *et al.* (1991) and Kang (1993) are not applicable since as prior art because they fail to teach or suggest the HIV-1 *tat* gene. It was asserted that the gene products described in these teachings are directed toward the HTLV-III/LAV *tat* gene which

differs from the HIV-1 *tat* gene. This position is clearly untenable in view of the prior art. Several different isolates of HIV-1 were originally identified and these were designated HTLV-III, LAV, and ARV. A uniform nomenclature was later developed and it was decided to call this group of viruses the human immunodeficiency viruses, or HIV. Both Haseltine *et al.* (1991) and Kang (1993) describe the preparation, expression, and purification of the HIV-1 *tat* gene. Thus, they are directly applicable as prior art.

Applicants further argue that Kang (1993) fails to teach or suggest the HIV-1 *tat* gene. Applicants are directed toward the second paragraph of column 8 wherein the inventor clearly and unambiguously states that "the tat protein of HIV-1 has also been produced by similar techniques. The recombinant baculovirus capable of producing the tat protein (AcNPV-tatYK) has been deposited at the American Type Culture Collection under the terms of the Budhapest Treaty and the deposit is identified by the number ATCC VR 2206." Thus, this Kang must have been in possession of the HIV-1 Tat gene since it was deposited at the ATCC. Thus, this portion of applicants' argument is also untenable in view of the prior art.

Applicants further submit the teachings of Georgiou *et al.* (1994) and Brey *et al.* (1992) would not render the claimed invention *prima facie* obvious, particularly since they were directed toward non-HIV-1 antigens. This reasoning is also unpersuasive. The prior art clearly illustrates that attenuated Salmonella expression vectors are useful for generating strong humoral and cellular immune responses against a heterologous antigen when said antigen is expressed on the bacterial surface, preferably as a stable lpp-OmpA-fusion protein. Contrary to applicants' assertion, one of ordinary skill in the art would

expect a heterologous antigen, absent evidence to the contrary, to generate a strong immune response in any given host when the recombinant salmonella vaccine vector is administered. This is totally consistent with the teachings of the prior art.

Finally, a declaration was provided by Dr. George B. Kitto, one of the named inventors, under 37 C.F.R. § 1.132 illustrating that attenuated *Salmonella* vaccine vectors expressing the HIV-1 RT are capable of inducing CTL responses against said viral antigen. This finding is not unexpected, considering the teachings of the prior art. The various references relied upon clearly demonstrate that attenuated *Salmonella* vaccine vectors encoding heterologous inserts are capable of inducing strong humoral and cell-mediated immune responses against the insert of interest.

Applicants' arguments have been carefully considered but are not deemed to be persuasive. As set forth *supra*, all of the components employed by the applicants (e.g., attenuated bacterial host, surface exposure fusion antigen, and viral transactivating protein were well-known in the prior art. Both the bacterial host and fusion protein had already been used to produce recombinant proteins. Moreover, viral transactivating proteins have been cloned, sequenced, and expressed in disparate expression systems. Therefore, there was a reasonable expectation of success of sufficient motivation for combining the aforementioned references.

7. Claims 1, 2, and 5-11[1] are rejected under 35 U.S.C. § 103(a) as

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[1] As previously set forth, the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious

being obvious over Hone *et al.* (1996) in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). Hone and colleagues provide attenuated *Salmonella typhimurium* vaccine vectors containing expression vectors encoding *Escherichia coli* OmpA::HIV-1 gp120 fusion proteins. These Salmonella strains induced both mucosal and systemic HIV-1 gp120-specific immune responses. The authors concluded (see Abstract, p. 203) that "These results, therefore, support the proposal that *Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments." The authors also noted (p. 206, penultimate paragraph) that "It is reasonable to propose, therefore, that *Salmonella* bearing surface-expressed rgp120 will elicit gp120-specific $CD8^+$ CTLs." This teaching does not disclose Lpp-OmpA-HIV-1 Tat fusion proteins.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative

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genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene.

Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. For instance, see columns 3-7 of the Haseltine publication wherein the gene, expression vectors, and cell lines producing said protein are described. The Kang publication describes the preparation of HIV-1 Tat-expressing recombinant baculoviruses (see col 8, first paragraph). Finally, Rodman describes the preparation of recombinant Tat and its utilization in ELISA assays (see col. 15). Thus, these teachings all illustrate that HIV-1 Tat was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Hone *et al.* (1996), since Hone and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are

expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Response to Arguments

8. Applicants traverse and submit that the combination of references do not render the claimed invention obvious and that there was no reasonable expectation of success. Applicants' argue that Haseltine *et al.* (1991) and Kang (1993) are not applicable since as prior art because they fail to teach or suggest the HIV-1 *tat* gene. It was asserted that the gene products described in these teachings are directed toward the HTLV-III/LAV *tat* gene which differs from the HIV-1 *tat* gene. This position is clearly untenable in view of the prior art. Several different isolates of HIV-1 were originally identified and these were designated HTLV-III, LAV, and ARV. A uniform nomenclature was later developed and it was decided to call this group of viruses the human immunodeficiency viruses, or HIV. Both Haseltine *et al.* (1991) and Kang (1993) describe the preparation, expression, and purification of the HIV-1 *tat* gene. Thus, they are directly applicable as prior art.

Applicants further argue that Kang (1993) fails to teach or suggest the HIV-1 *tat* gene. Applicants are directed toward the second paragraph of column 8 wherein the inventor clearly and unambiguously states that "the tat protein of HIV-1 has also been produced by similar techniques. The recombinant baculovirus capable of producing the tat protein (AcNPV-tatYK) has been deposited at the American Type Culture Collection under the terms of the Budhapest Treaty and the deposit is identified by the number ATCC VR 2206." Thus, this Kang must have been in possession of the HIV-1 Tat gene since it was deposited at the ATCC. Thus, this portion of applicants' argument is also untenable in view of the

prior art.

Applicants further submit the teachings of Georgiou *et al.* (1994) and Brey *et al.* (1992) would not render the claimed invention *prima facie* obvious, particularly since they were directed toward non-HIV-1 antigens. This reasoning is also unpersuasive. The prior art clearly illustrates that attenuated Salmonella expression vectors are useful for generating strong humoral and cellular immune responses against a heterologous antigen when said antigen is expressed on the bacterial surface, preferably as a stable lpp-OmpA-fusion protein. Contrary to applicants' assertion, one of ordinary skill in the art would expect a heterologous antigen, absent evidence to the contrary, to generate a strong immune response in any given host when the recombinant salmonella vaccine vector is administered. This is totally consistent with the teachings of the prior art.

Applicants also argue that Hone *et al.* (1996) fail to suggest that cellular immune responses can be induced against HIV-1 using the recombinant *Salmonella* vectors. This argument is not persuasive because Hone and colleagues clearly state (see Abstract, p. 203) that "These results, therefore, support the proposal that *Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elucidation of HIV-specific T cells in, the mucosal and systemic compartments" and (penultimate paragraph, p. 206) "It is reasonable to propose, therefore, that *Salmonella* bearing surface-expressed rgp120 will elicit gp120-specific $CD8^+$ CTLs." Thus, contrary to applicants' assertion, there is a reasonable expectation that strong humoral and cell-mediated immune responses will be generated against HIV-1 antigens expressed in this system.

Finally, a declaration was provided by Dr. George B. Kitto, one of the named inventors, under 37 C.F.R. § 1.132 illustrating that

attenuated *Salmonella* vaccine vectors expressing the HIV-1 RT are capable of inducing CTL responses against said viral antigen. This finding is not unexpected, considering the teachings of the prior art. The various references relied upon clearly demonstrate that attenuated *Salmonella* vaccine vectors encoding heterologous inserts are capable of inducing strong humoral and cell-mediated immune responses against the insert of interest.

Applicants' arguments have been carefully considered but are not deemed to be persuasive. As set forth *supra*, all of the components employed by the applicants (e.g., attenuated bacterial host, surface exposure fusion antigen, and viral transactivating protein were well-known in the prior art. Both the bacterial host and fusion protein had already been used to produce recombinant proteins. Moreover, viral transactivating proteins have been cloned, sequenced, and expressed in disparate expression systems. Therefore, there was a reasonable expectation of success of sufficient motivation for combining the aforementioned references.

Finality of Office Action

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 C.F.R. § 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 C.F.R. § 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 C.F.R. § 1.114. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO**

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

10. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

11. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

31 May, 2003

PRIMARY EXAMINER